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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,438	06/25/2007	Raymond Nadeson	210174.401USPC	9722

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EXAMINER	
RAO, SAVITHA M	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,438	NADESON ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-49 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-49 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 43-49 and 51 are pending.

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on 12/01/2010 are acknowledged. Claims 43 and 49 are amended, Claim 50 is cancelled and new claim 51 is added. Claims under consideration in the instant office action are claims 43-49 and 51

Applicants' arguments, filed 12/01/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 4th Paragraph

The following is a quotation of the fourth paragraph of 35 U.S.C. 112:

> Subject to the following paragraph, a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

Claim 51 is rejected under 35 USC § 112 4th Paragraph as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim 51, or amend the claim 51to place the claim 51in proper dependent form, or rewrite the claim(s) in independent form. Claim 51 recites the "wherein the neuropathic pain is associated with …….. Vertebral Ankylosing Hyperostosis". Among the list of neuropathic associated diseases are conditions such

as alopecia, ataxia telengiactasi, multiple myeloma etc. which are cancer associated neuropathic pain which is excluded in claim 43 upon which claim 51 depends on. Accordingly, many of the neuropathic pain listed in new claim 51 are associated with Cancer and as such fails to further limit the neuropathic pain recited in instant claim 43.

Claim Rejections - 35 USC § 103

New Grounds of Rejection necessitated by the amendment filed on 12/01/2010

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicants' are advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim

that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 43-45, 48- 49 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al. (US 5,521,178). in view of Williams et al. (US 2004/0076648) and Chizh et al. (US 2004/0092531).

Nickel et al. teach that flupirtine is an analgesic with muscle-relaxing components of action (col.2, lines 1-3) and teach administration of flupirtine in combination with morphine for treatment of pain wherein it was demonstrated that the combination provided an increase in analgesic activity and furthermore flupirtine weakens morphine induced tolerance, physical dependence and behavior changes (col.2, lines 45-50). Finally Nickel et al. discloses a method of providing an analgesic effect in a patient in need therefor which comprises concurrently administering 5 mg/kg of flupirtine and 2.5 mg/kg to 10 mg/kg morphine , wherein the analgesic effect of morphine is preserved and potential for developing chemical dependence on the morphine is reduced in the patient (reference claim 3).

Nickel et al. fails to teach that the analgesic effect of the combination is on neuropathic pain.

However, Williams et al. teaches that compositions and methods of treating neuropathic pain with a combination of anti-depressant and a NMDA receptor antagonist [0052-0054]. William's et al. teaches "flupirtine" and "ketamine" as the NMDA receptor antagonists useful in their invention([0093] and [0106] and teaches the

concentration of the NMDA receptor antagonists in their inventive composition to be 0.1% to 5% of the total weight of the composition [0109]. Williams et al, their inventive compositions to be useful in the method of treating pain related to or induced by the following diseases, trauma, or conditions: general neuropathic conditions, which includes **peripheral neuropathy**, reflex-sympathetic dystrophy, and painful scar; **specific neuralgias at any location of the body**; **back pain**; **diabetic neuropathy;** alcoholic neuropathy; metabolic neuropathy; inflammatory neuropathy; **chemotherapy-induced neuropathy**, herpetic neuralgias; spinal-cord-injury; stroke; fibromyalgia; burns involving nerve damage; **AIDS-related pain syndromes**; connective tissue disorders, such as systemic lupus erythematosis, systemic sclerosis, polymyositis, and dermatomyositis; and inflammatory conditions, such as acute inflammation (e.g. trauma, surgery and infection) or chronic inflammation among others [0054]. Williams et al. further teaches that their compositions can additionally include local anesthetics, which include opioids such as morphine [0138 and 0140]. Accordingly, Williams et al. provides one of ordinary skill in the art motivation to utilize flupirtine in combination with opioids in the treatment of neuropathic pain.

Further, Chizh et al. teaches a combination of active ingredients which comprises at least on opioid compound with the fentanyl-type structure and a ketamine which is an NMDA antagonist [0009] and [0004] and their ability to show a lasting analgesic effect in controlling pain especially for controlling neuropathic pain [0014 and 0031]. Chizh et al. discloses that the undesirable side effect which occurs with the administration of either the NMDA antagonist alone or the opioid alone does not occur or occurs for a

considerable shorter period of time when the two are administered together [0003-0004] and [0014]. Chizh et al. teaches that the medicament formulation of their invention is suitable for oral, intravenous, transdermal etc administration [0035]. Finally Chizh et al. teaches that the lasting analgesic effect of their inventive composition has the advantage that the daily dose of active components a)fentanyl and b)Ketamine required for effective pain control can be reduced consequently reducing undesirable side effects which usually occur with the administration of active components fentanyl or ketamine singly, such as respiratory depression, vomiting, dependency, sedation, constipation, the development of tolerance, hallucinogenic effects, impaired coordination, or itching [0051].

In view of the foregoing references, It would have been prima facia obvious to employ the combination of flupirtine and an opioid analgesic, such as morphine for the treatment of neuropathic pain, motivated by the teaching of Nickel et al. who teach that flupirtine is a centrally acting analgesic (see introduction) that enhances the analgesic effects of opioids, such as morphine for treatment of pain, and the teaching of Williams et al who teaches the effectiveness of flupirtine (NMDA antagonist) in the treatment of neuropathic pain and Chizh et al. who teaches the combination of an opioid such as fentanyl and an NMDA antagonists ketamine to be useful in the treatment of neuropathic pain. Motivation, comes from the prior art teachings that the NMDA antagonists such as ketamine when used in combination with opioid reduces the side effects associated with the opioid (Chizh et al.) and that flupirtine which is a NMDA antagonist (William et al.) weakens morphine induced tolerance, physical dependence

and behavior changes (Nickel et al.) Accordingly, One skilled in the art, such as a pain management specialist, would have been motivated to employ the combination of flupirtine and morphine taught by Nickel et al. for the treatment of neuropathic pain, motivated by the teachings of Nickel et al., William et al. and Chizh et al. with a reasonable expectation of success that such a treatment protocol would result in enhanced analgesic activity against neuropathic pain with reduced side effects.

Moreover, both flupirtine and opioid analgesics are individually known in the art as agents for treating neuropathic pain (as taught by the references above) whose efficacy when administered alone is well established for the treatment of a neuropathic pain arising due to varied conditions. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In re Kerkhoven, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. In re Crockett, 126 U.S.P.Q. 186, 188 (CCPA 1960). Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed supra). The natural presumption that two individually known analgesic drugs would, when combined, provide a third composition also useful for treating neuropathic pain flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (e.g. unexpected results) to rebut this natural presumption. Further, it is clear from the prior art that flupirtine potentiates the analgesic effect of opioid such as

morphine and NMDA antagonist (ketamine, flupirtine) when used in combination with an opioid (fentanyl) decreases side effects, thereby increasing efficacy One skilled in the art would have been imbued with at least a reasonable expectation that flupirtine would also potentiate the effect of the morphine in the treatment of neuropathic pain.

In re Diamond and Kellman, 149 USPQ 562 (C.C.P.A. 1966), supports the obviousness of combining two drugs known to be useful for the same purpose. In *Diamond*, Appellants were claiming a combination of adenosine-5-monophosphate (A5MP) and a glucocorticoid. The Examiner cited prior art teaching that A5MP and glucocorticoids were known in the art to be useful for treating collagen diseases and that combining drugs for the treatment of disease is suggested by the prior art. Appellants argued that the combination of the two drugs is non-obvious since there is no teaching to combine these two out of all known anti-inflammatory agents. The Court was not persuaded by this argument, stating that: explicitly from the reference itself.

> "...we think it clear that it is a standard practice in this art to combine ingredients."
> "We are not convinced of non-obviousness of the combination of the two drugs, A5MP and a glucocorticoid such as hydrocortisone, for use as an anti-inflammatory composition, particularly since the record supports the solicitor's contention that the drugs selected are two of the commonly used drugs in the treatment of such collagen diseases."

With regards to instant claim 44, Chizh et al. teaches the concomitant administration of fentanyl and ketamine and accordingly, it would have been obvious to an ordinarily skilled artisan to optimize the sequence of administration of the two drugs in an effort to obtain maximum benefit.

Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al. (US 5,521,178). in view of Williams et al. (US 2004/0076648) and Chizh et al. (US 2004/0092531) as applied to claims 43-45, 48-49 and 51 above, and further in view of, and further in view of Perovic et al (Neurodegeneration, Vol. 4 pages 369-374 (1995), reference already of record)).

Nickel et al., William et al. and Chizh et al. fails to teach the limitation wherein the opioid does not induce overt sedation in the presence of flupirtine.

However, Perovic et al. teach that flupirtine is a clinically safe compound with drowsiness reported in only 10% of cases (page 373, column 2). Since the dosage of the opioid is not disclosed, then the claim encompasses an almost negligible amount of opioid and as such overt sedation would not occur since it is dose related.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ a non sedating combination of flupirtine and an opioid motivated by the teaching of Perovic et al. that flupirtine caused drowsiness in only 10 % of cases combined with the well known fact that sedation of opioid analgesics is dose related and since the claims do not disclose the dosage, they encompass a negligible amount of opioid. Further, Nickel et al. teach that flupirtine weakens morphine induced behavior changes (see methods/results). One having ordinary skill in the art at the time the invention was made would reasonably deduce that sedation is one of the primary behavior changes that morphine induces.

Response to applicant's arguments filed on 12/01/2010:

In light of the new grounds of rejection above, the arguments submitted on 12/01/2010 which was for the previously submitted rejection is moot.

Conclusion

Claims 43-49 and 51 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
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